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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,985	12/19/2001	Carine Capiau	B45182	2966

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,985	CAPIAU ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11,12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) *12,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed March 10, 2003. Claims 1-4 and 6 have been amended. Claim 5 has been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and Response, the following rejections have been withdrawn:

a) Rejection of claims 1-9 and 11 under 35 U.S.C. 112, first paragraph, paragraph 2, pages 1-7 of the previous Office action.

b) Rejections of claims 1-9 and 11 under 35 U.S.C. 112, second paragraph, paragraphs 3 and 4, page 7 of the previous Office action.

c) Rejections of claims 1-9 and 11 under 35 U.S.C. 103(a), paragraph 5, pages 8-10 of the previous Office action.

Rejections Maintained

4. The rejection of claims under 35 U.S.C. 103(a) as unpatenable over Kuo et al in view of Masure et al maintained for the reasons set forth in paragraph 6, pages 10-11 of the previous Office Action.

The rejection was on the grounds that Kuo et al teach a composition comprising immunogenic polysaccharide-protein conjugates and pneumolysin protein of *Streptococcus pneumoniae* (see the Abstract). Kuo et al teach that capsular polysaccharides of various pneumococcal types (for example, types 6B, 14C, 18C and 20) are used in their inventions (column 5, lines 17-28 and column 6, Example 1). Kuo et al teach that the composition may be added to immunologically acceptable diluents or carriers in the conventional manner to prepare injectable liquid solutions or suspensions (column 5, lines 45-47). Kuo et al teach that the conjugates of the invention may be bound to aluminum hydroxide, aluminum phosphate (alum), QS-21, monophosphoryl lipid A and deacylated monophosphoryl lipid A (which induce strong TH1 responses) (column 5 lines 47-51). It is well known in the art to add protein carriers such as keyhole limpet haemocyanin (KLH), diphtheria toxoid, tetanus toxoid and protein derivative of Tuberculin (PPD) to antigens to enhance the immunogenicity of the antigen this is evidenced by *(U.S. Patent No. 6,419,932, U.S. Patent No. 4, 761, 283, U.S. Patent No. 6,224,880 and U.S. Patent No. 5,360,897).*

Kuo et al do not teach choline binding proteins.

Masure et al teach a vaccine comprising choline binding proteins (CBPs) (column 6, lines 65-67 and column 7, lines 1-8). Masure et al teach vaccines comprising CBP antigen or antigenic derivative or fragment thereof or a CBP nucleic acid vaccine that can be administered via any parenteral route including but not limited to intramuscular, intraperitoneal, intravenous and the like (column 24, lines 57-61). Masure et al suggest that criteria to consider in selecting a preferred CBP as a vaccine candidate includes testing CBP defective mutants for attenuation of virulence in animal models for bacteremia or colonization efficacy alone or in combination or coupled to a capsular polysaccharide (column 14, lines 41-46). Masure et al teach that the vaccines of the invention can be comprises an active material such as a diluent (i.e. carrier or vehicle) (column 29, lines 14-20). Masure et al teach that CBP or fragment thereof can be conjugated to an immunogenic carrier, e.g. bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) (column 22, lines 5-8).

It would be *prima facie* obvious at the time the invention was made to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al would be effective in treating *Streptococcus pneumoniae* infections.

R sponse to Applicant's Arguments

5. The Examiner has addressed Applicant's arguments below:

Applicant urges that the claims are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen and an adjuvant which is a preferential inducer of a TH1 response.

The Examiner disagrees with this assertion. For clarification of the record, Kuo et al teach a composition comprising an immunogenic polysaccharide-protein conjugate, wherein the protein used in the polysaccharide-protein conjugate is pneumolysin in combination with the adjuvant, deacylated monophosphoryl lipid A (column 5, lines 45-53). Kuo et al do not teach the addition, a *Streptococcus pneumoniae* protein antigen.

Applicant urges that the "inventive concept of Kuo et al is that the native pneumolysin, a toxin is not detoxified prior to conjugation.

It is the Examiner's position that Applicant's agreement regarding the inventive concept of Kuo et al are irrelevant to the claimed invention. The claims require that the immunogenic composition comprises: A) at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate, B) at least one *Streptococcus pneumoniae* protein antigen and C) an adjuvant which is a preferential inducer of a TH1 response. Kuo et al teach a *Streptococcus pneumoniae* polysaccharide-protein conjugate and an adjuvant which is a preferential inducer of a TH1 response.

Applicant urges that Kuo et al teach that any adjuvant can be used which is in contrast to the claimed invention and that Kuo et al do not teach a preferential inducer of a TH1 response.

The Examiner disagrees with this assertion. The claims require that the immunogenic composition require: A) at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate B) at least one *Streptococcus pneumoniae* protein antigen and C) an adjuvant which is a preferential inducer of a TH1 response. Kuo et al teach an adjuvant which is a preferential inducer of a TH1 response, deacylated monophosphoryl lipid A.

Applicant urges that Kuo et al do not teach a free or unconjugated protein in combination with pneumococcal polysaccharide conjugates(s).

It is the Examiner's position that Applicant is arguing limitations that are not in the claims. The claims are drawn to an immunogenic composition comprising: A) at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate B) at least one *Streptococcus pneumoniae* protein antigen and C) an adjuvant which is a preferential inducer of a TH1 response. There is not claim limitation that requires that the *S. pneumoniae* protein antigen is free or unconjugated. For clarification of the record Kuo et al do not teach a three-component composition. The missing element is "B" and the claim does not require this to be "free or unconjugated.

Applicant urges that Masure et al do not address the deficiencies of Kuo et al. Applicant urges that Masure et al teach as a whole that choline binding proteins are a suitable alternative to polysaccharides in developing a pneumoncoccal vaccine.

The Examiner disagrees with this assertion. The claims are drawn to an immunogenic composition comprising: A) at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate, B) at least one *Streptococcus pneumoniae* protein antigen and C) an adjuvant which is a preferential inducer of a TH1 response. Masure et al meets the deficiencies of Kuo et al by teaching a *Streptococcus pneumoniae* protein antigen, in particular, choline binding proteins (CBP). Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection (column 30, lines 34-42). Therefore, CBPs are not merely alternatives to polysaccharides but can be used in combination with other vaccines for treating bacterial infection. The combination of references meet the claim limitations.

Applicant urges that Masure et al is not an effective reference as it is issued after Applicant's U.S. filing later of March 17, 2000.

The Examiner disagrees with this assertion. Masure et al is a 102(e) reference because it is a U.S. Patent which has an effective filing date of May 1, 1997. The MPEP at section 2141.01 states that "A 35 U.S.C. 103 rejection is based on 35 U.S.C. 102(a), 102(b), 102(e), etc. depending on the type of prior art reference used and its publication or issue date. For instance, an obviousness rejection over a U.S. patent which was issued more than 1 year before the filing date of the application is said to be a statutory bar just as if it anticipated the claims under 35 U.S.C. 102(b). Analogously, an obviousness rejection based on a publication which would be applied under 102(a) if it anticipated the claims can be overcome by swearing behind the publication date of the

reference by filing an affidavit or declaration under 37 CFR 1.131. For an overview of what constitutes prior art under 35 U.S.C. 102, see MPEP § 901 - § 901.06(d) and § 2121 - § 2129". Therefore, Masure et al was used as a 102(e) reference in a 35 U.S.C. 103(a) rejection.

Applicant urges that none of the reference alone or in combination teach an enhanced immune response when a polysaccharide + protein (free) + adjuvant (which is a preferential inducer of a TH1 response) is combined. None of the references alone or in combination teach stimulation of the immune response in the same manner (humoral response and cell-mediated immunity) as Applicants. Applicant urges that none of the reference alone or in combination teach an enhanced effect and none of the references alone or in combination teach stimulation of the immune response in the same manner as Applicants.

The Examiner disagrees with this assertion. The claims are drawn to an immunogenic composition comprising: A) at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate, B) at least one *Streptococcus pneumoniae* protein antigen and C) an adjuvant which is a preferential inducer of a TH1 response. Kuo et al teach at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate and an adjuvant which is a preferential inducer of a TH1 response used for immunization against pneumococcal infections. Kuo et al do not teach at least one *Streptococcus pneumoniae* protein antigen. Masure et al teach a *Streptococcus pneumoniae* protein antigen, in particular, choline binding proteins which are used in anti-pneumococcal vaccines. Masure et al teach that one may administer the CBP vaccines in conjunction

with one or more pharmaceutical compositions used for treating bacterial infection (column 30, lines 34-42). It would have been obvious to one of skill in the art at the time the invention was made to add the *Streptococcus pneumoniae* protein antigen (choline binding proteins) of Masure et al to the vaccine compositions of Kuo et al comprising the *Streptococcus pneumoniae* polysaccharide-protein conjugate and an adjuvant which is a preferential inducer of a TH1 response used for immunization against pneumococcal infections because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection (column 30, lines 34-42). One would be motivated to use the *Streptococcus pneumoniae* polysaccharide-protein conjugate and an adjuvant which is a preferential inducer of a TH1 response of Kuo et al in combination with the *Streptococcus pneumoniae* protein antigen (choline binding proteins) of Masure et al because both have been shown to be protective against *Streptococcus pneumoniae* infections.

Regarding Applicant's assertion, "Applicant urges that none of the reference alone or in combination teach an enhanced immune response when a polysaccharide + protein (free) + adjuvant (which is a preferential inducer of a TH1 response) is combined", as indicated above, Applicant is arguing limitations that are not in the claims. There is no claim limitation that requires that the *S. pneumoniae* protein is free or unconjugated. The claims required components are at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate, at least one *Streptococcus pneumoniae* protein antigen and an adjuvant which is a preferential inducer of a TH1 response.

Regarding Applicant's assertions, "None of the references alone or in combination teach stimulation of the immune response in the same manner (humoral response and cell-mediated immunity) as Applicants and none of the reference alone or in combination teach an enhanced effect, the claimed invention only requires that a stimulation is made, the stimulation does not have to be an "enhanced stimulation". Applicant has not provided a side-by-side comparison of the combined vaccine composition as taught by the prior art with that of the claimed invention, therefore it cannot be determined if the claimed vaccine differs in stimulating the immune system from that of the prior art as combined above.

There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Examiner
May 10, 2003

PATRICIA A. DUFFY
PRIMARY EXAMINER